REMARKS

Claims 88-107 were originally pending in this application. As a result of a restriction requirement mailed on July 7, 2010, claims 88-95 were elected. Presently, claims 88 and 94 have been amended, claims 89-93 and 95 have been canceled, claims 108 – 113 have been added and claims 110-113 are presumed withdrawn as directed to a non-elected invention. No new matter has been added as a result of these amendments and claims 88, 94, 108-109 are currently pending.

Rejections under 35 U.S.C. §112, first paragraph:

Written Description

The Office Action stated that claims 88-95 were rejected as not demonstrating that the inventor had possession of the claimed invention at the time the application was filed. Specifically, the Office Action states that the size of the claimed genus was "phenomenal" and that the description of approximately 17 compounds falling within the claimed genus was not sufficient to support claims of that breadth.

Without admitting to the propriety of this rejection, Applicants note that currently pending amended claims 88, 94, 108 and 109 are limited to methods of vaccinating a patient using a combination of a polyhydroxylated pyrrolizidine alkaloid administered with a neoantigen and a toll-like receptor ligand. The specification as filed contains no less than 15 examples of polyhydroxylated pyrrolizidine alkaloid compounds as well as numerous neoantigen and toll-like receptor ligand examples throughout the specification. Thus, Applicant asserts that this amended genus is adequately supported (please see the specification as filed including pages 4, 5, 6, 7, 20, 23-30, and 48-50).

Enablement

The Office Action also rejected claims 88-93 as not being enabled for "the use of any alkaloid to induce immunotherapy generally" (please see page 5 of the Office Action).

Applicant believes that the present amendments to the claims resolve the enablement issues stated in the Office Action. Regarding the scope of the claims, the currently pending claims are now limited to polyhydroxylated pyrrolizidine alkaloids administered in combination with a neoantigen and a toll-like receptor ligand. There is ample support throughout the specification for such a genus including pages 4, 5, 6, 7, 20, 23-30, and 48-50.

Regarding the amount of direction or guidance provided and the presence or absence of working examples, Applicant respectfully asserts that there may be confusion regarding the data shown on pages 48-50 of the specification as filed. That data is directed toward whether or not a particular alkaloid compound induces production of interleukin (IL)-12, not IL-2. The stimulation of IL-12 production is not a required feature of the alkaloids of the present invention. Rather, as stated on pages 30 and 31 of the specification IL-12 stimulation is an optional feature of certain preferred embodiments of the present invention. Further, and with regard to the quantity of experimentation necessary, the members of the presently amended genus are either represented in the specification as filed or easily ascertainable by methods known in the art and briefly described on page 23 of the specification. While the art in general is arguably unpredictable in some ways, the methods necessary to identify members of the presently claimed genus are routine and not unpredictable in their application.

For the above reasons, the Applicants respectfully assert that the presently pending claims do meet the requirements of 35 U.S.C. §112.

Rejections under 35 U.S.C. §103:

The Office Action states that claims 88-95 are rejected under 35 U.S.C. §103(a) as unpatentable over Shizuo Akira, *Mammalian Toll-Like Receptors*, 15 CURR. OPIN. IMMUNOL. 5, 8, 9 (February 2003) (hereinafter "Akira"), in view of Ruain Xu et al., *Molecular Therapeutics of HBV*, 3 CURR. GENE THERAPY 341 (2003) (hereinafter "Xu"), Alison Watson et al., *Polyhydroxylated Alkaloids – Natural Occurrence and Therapeutic Applications*, 56 PHYTOCHEM. 265 (2001) (hereinafter "Watson"), as evidenced by Andrew Bell et al., *Synthesis of Casuarines [Pentahydroxylated Pyrrolizidines] by Sodium Hydrogen Telluride-Induced Cyclisations of Azidodimesylates*, 38 TET. LET. 5869 (1997) (hereinafter "Bell").

The present claims have been amended to include only methods of vaccination with a polyhydroxylated pyrrolizidine alkaloid, a neoantigen, and a toll-like receptor ligand. With regard to the general threshold matters described on pages 9-10 of the Office Action, the scope of the claims has been altered significantly in terms of: the genus of compounds claimed, the necessary response by the patient (i.e. induction of IL-2 production in dendritic cells), and the specific type of immune response claimed (vaccination). Therefore, Applicants believe that these matters have been addressed in their entirety.

With regard to the Akira reference, the Office Action states that this reference "indicates that exposing immune systems to certain bacterial, fungal, and viral TLR ligands would induce an immune response by promoting the production of cytokines and other cellular signaling media." As also pointed out in the Office Action, Akira fails to "discuss or provide a rationale for combining immunotherapy directed to bacterial, fungal, or viral infections by administering a combination of a TLR ligand and a polyhydroxylated alkaloid" (please see page 11 of the Office Action). Akira is focused on the specific nature of particular toll-like receptors and their evolutionary development, with some mention of known or suspected signal transduction pathways. The discussion in Akira is not of particular relevance to the presently claimed invention. Additionally, stimulation of IL-2 production by dendritic cells is not discussed or even hinted at in Akira, in fact, IL-2 itself is not mentioned or implicated in the Akira reference. Further, Akira does not discuss or provide a rational for combining a polyhydroxylated pyrrolizidine alkaloid, a neoantigen, and a toll-like receptor ligand to vaccinate a patient, as required by the present claims.

The Office Action states that the Xu reference "describes a variety of approaches to promoting improved immunotherapy, including not only direct antiviral strategies, but also the modulation of the immune system of the subject to be treated" (please see page 11 of the Office Action). The Xu reference is focused on the use of gene therapy as a way to stimulate production of endogenous immune material and this is not relevant to the present amended claims, which include no gene therapies. Further, nothing in Xu remedies the deficiencies found in Akira, namely, there is no indication that use of a polyhydroxylated pyrrolizidine alkaloid, a neoantigen and a toll-like receptor ligand would result in a prolonged and pronounced stimulation of IL-2

production in the dendritic cells of a patient nor is there any indication of the desirability of using this combination of compounds in a method of vaccination.

The Office Action further states that the Watson reference indicates "that a variety of polyhydroxylated alkaloids, including casuarine and swainsonine, act as potent, reversible, and competitive glycosidase inhibitors" and that "owing to this activity, polyhydroxylated alkaloids such as casuarine would find utility as immune-stimulants, anti-viral agents, and general anti-infective agents" (please see pages 11-12 of the Office Action). The Office Action states that the Bell reference echoes the findings of Watsonwith regard to the casuarine's activity as an inhibitor of glycosidases and glucosidase in particular (please see page 12 of the Office Action). With respect to the Watson and Bell references, neither reference remedies the deficiencies of both Akira and Xu with respect to the presently claimed invention. Specifically, neither Watson nor Bell teach vaccination of a patient through the use of a polyhydroxylated pyrrolizidine alkaloid along with a neoantigen and a toll-like receptor ligand wherein IL-2 production is stimulated in the dendritic cells of the patient. Characterization of some polyhydroxylated alkaloids as glycosidase inhibitors provides no indication of their use as vaccinating agents capable of inducing IL-2 production from dendritic cells when co-administered with a neoantigen and a toll-like receptor ligand.

In summary, the cited references of Akira, Xu, Watson and Bell do not provide teachings sufficient to render the presently claimed invention obvious under 35 U.S.C. §103(a). None of the cited references discusses the vaccination of a patient using a combination of a polyhydroxylated pyrrolizidine alkaloid along with a neoantigen and a toll-like receptor ligand. Further, none of the references teach the use of such a vaccinating agent as stimulating the production of IL-2 in the dendritic cells of the patient. For these reasons, Applicants respectfully assert that the presently outstanding rejection under 35 U.S.C. §103(a) is inapposite with regard to the presently pending amended claims.

As a result of the above discussion, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn with respect to the currently pending claims.

Double Patenting:

The Office Action stated that claims 88-95 are provisionally rejected on the grounds of non-statutory double patenting over two copending applications 1) 10/597,296, and 2) 10/543,014. As stated in the Office Action, a timely filed Terminal Disclaimer may be used to obviate such rejections. Applicants note the provisional nature of these rejections and will address them, if appropriate, at a time when one or both of the copending applications issue.

CONCLUSION

It is believed that the application is in condition for allowance, and such action is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, the Examiner is invited to telephone the undersigned attorney at the telephone number provided.

Respectfully submitted,

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